Refine Search

Search Results -

Terms	Documents
(liposome same inkjet) and (active or drug)	11

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L3

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Friday, January 18, 2008 Purge Queries | Printable Copy | Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L3	(liposome same inkjet) and (active or drug)	11	L3
L2	liposome same inkjet same (active or drug)	9	L2
L1	liposome same (nifedipine or verapamil or nitroglycerin or digoxin or timolol) same ethanol	8	L1

END OF SEARCH HISTORY

L6: Entry 20 of 20 File: USPT Dec 11, 1990

DOCUMENT-IDENTIFIER: US 4976964 A
TITLE: Medicament formulation containing dihydropyridines and a process for its preparation

Brief Summary Text (22):
Compoumds which may be mentioned particular are: nifedipine, nimodipine, nitrencipine and nisoldipine.

Brief Summary Paragraph Table (1):
TABLE 1

##STR2## No. X R.sup.1 R.sup.2 R.sup.3 Generic

1 2-NO.sub.2 CH.sub.3 CH.sub.3 CH.sub.3 Nifedipine 2 3-NO.sub.2 nPrOCH.sub.2 CH.sub.2 nPrOCH.sub.2 CH.sub.2 CH.sub.3 Niludipine 3 3-NO.sub.2 C.sub.2 H.sub.5 CH.sub.3 CH.sub.3 Nitrendipine 4 2-NO.sub.2 CH.sub.3 (CH.sub.3).sub.2 CHCH.sub.2 CH.sub.3 Nisoldipine 5 3-NO.sub.2 CH(CH.sub.3).sub.2 (CH.sub.2).sub.2OCH.sub.3 CH.sub.3 Nimodipine 6 3-NO.sub.2 C.sub.2 H.sub.5 C.sub.10 H.sub.21 (n) CH.sub.3 7 2-Cl CH.sub.3 CH.sub.2CF.sub.3 CH.sub.3 8 2-Cl C.sub.2 H.sub.5 CH.sub.2CF.sub.3 CH.sub.3 9 3-NO.sub.2 CH(CH.sub.3).sub.2 n-PrOCH.sub.2 CH.sub.2 CH.sub.3 10 3-NO.sub.2 CH.sub.3 C.sub.6 H.sub.5 CH.sub.2 N(CH.sub.3)CH.sub.2 CH.sub.2 CH.sub.3 Nicardipine 11 2,3-Cl.sub.2 C.sub.2 H.sub.5 CH.sub.3 CH.sub.3 Felodipine 12 2,3CON C.sub.2 H.sub.5 C.sub.2 H.sub.5 CH.sub.3 13 2,3NON CH.sub.3 CH(CH.sub.3).sub.2 CH.sub.3 14 3-NO.sub.2 C.sub.2 H.sub.5 C.sub.2 H.sub.5 CH.sub.2 OH 15 3-NO.sub.2 CH.sub.3 CH.sub.3 CN

n-Pr = nPropyl

Detailed Description Text (17):
A chloroform solution of 100 mg of egg lecithin, 8 mg of dicetyl phosphate and 5 mg of nifedipine is evaporated, while gassing with argon. After addition of 10 ml of 0.1 M Na phosphate buffer, pH 7.3, the mixture is subjected to ultrasonic treatment at 40.degree. -45.degree. C. under Na light for 10 minutes.

Detailed Description Text (28):
150 g of egg lecithin and 1 g of nimodipine are dissolved in 200 ml of ethanol. The solvent is evaporated at 50.degree.-60.degree. C. 5 l of an aqueous citrate buffer (pH=6.7) are added to the dry substance thus prepared. The buffer contains 4.7% of D-mannitol. After an incubation time of about 24 hours, the vessel containing the solid and the aqueous phase is shaken thoroughly, a crude dispersion forming. This crude dispersion is further dispersed in a high-pressure homogenizer. The apparatus used (jet disperser) operates under a pressure of 250 bar. It allows circulatory operation (recycling of the discharged material into the inlet channel). After 20 passes, a liposome dispersion with an average particle size of 163 nm is obtained.

Current US Original Classification (1):
424/450

Other Reference Publication (1):
Chemical Abstracts, Band 91, 1979, Columbus, Ohio, USA, Y. Matsuno et al.,

"Lolubilizotion of nifedipine" Seite 350, Spalte 1, Zusammenfassung-Nr. 163 057s & Jpn. Kokai Tokkyo Koho, 79-55 714, Ota Pharmaceutical Co. Ltd.; Tokai Capsule Co., Ltd.

Previous Doc Next Doc Go to Doc#

Refine Search

Search Results -

Terms	Documents
L5 and (verapamil or nitroglycerin or nifedipine)	20

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L6

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Friday, January 18, 2008 Purge Queries | Printable Copy | Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L6	L5 and (verapamil or nitroglycerin or nifedipine)	20	L6
L5	L2 and 424/450.ccls.	65	L5
L4	L3 and (ethanol or alcohol)	47	L4
L3	liposome adj10 jet$	96	L3
L2	liposome same jet$	409	L2
L1	liposome adj10 (spray or aerosol)	1613	L1

END OF SEARCH HISTORY

L1: Entry 6 of 8 File: USPT Jun 21, 1988

DOCUMENT-IDENTIFIER: US 4752425 A
TITLE: High-encapsulation liposome processing method

Detailed Description Text (13):
In addition, the lipid solution may contain lipophilic protective agents, such as .alpha.-tocopherol, and/or lipophilic drug compounds which are to be entrapped in the lipid bilayer phase of the liposomes. Representative lipophilic compounds which can be administered in liposome-entrapped form include protagladins, amphotericin B, progesterone, isosorbide dinitrate, testosterone, nitroglycerin, estradiol, cortisone, dexamethasome and related esters, and betamethasone valerate. As indicated above, the lipid solvent may also contain the water-soluble compound to be encapsulated, where such cannot be included in the aqueous medium used in forming the liposomes. As an example, studies conducted in support of the present invention, and discussed below, show that the water-soluble compound propranolol causes liposome disruption when originally dissolved in the aqueous medium used in the solvent injection method. However, when dissolved in the lipid solvent (Freon 11:ethanol, 10:1), liposomes with very high encapsulated propranolol are formed.

Hit List

First Hit | Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 9 of 9 returned.

☐ 1. Document ID: US 20070184489 A1

L2: Entry 1 of 9 File: PGPB Aug 9, 2007

PGPUB-DOCUMENT-NUMBER: 20070184489
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20070184489 A1

TITLE: Compartmentalised combinatorial chemistry by microfluidic control

PUBLICATION-DATE: August 9, 2007

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Griffiths; Andrew	Cambridge	MA	GB
Weitz; David	Bolton	CT	US
Link; Darren	Guilford	MA	US
Ahn; Keunho	Boston		US
Bibette; Jerome	Paris		FR

US-CL-CURRENT: 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20070092914 A1

L2: Entry 2 of 9 File: PGPB Apr 26, 2007

PGPUB-DOCUMENT-NUMBER: 20070092914
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20070092914 A1

TITLE: Compartmentalised screening by microfluidic control

PUBLICATION-DATE: April 26, 2007

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Griffiths; Andrew	Cambridge	MA	GB
Weitz; David	Bolton	CT	US
Link; Darren	Guilford	MA	US
Ahn; Keunho	Boston		US

Bibette; Jerome Paris FR

US-CL-CURRENT: 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 3. Document ID: US 20060154298 A1

L2: Entry 3 of 9 File: PGPB Jul 13, 2006

PGPUB-DOCUMENT-NUMBER: 20060154298
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060154298 A1

TITLE: Method of synthesis and testing of combinatorial libraries using microcapsules

PUBLICATION-DATE: July 13, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Griffiths; Andrew David	Cambridge		GB
Abell; Chris	Cambridge		GB
Hollfelder; Florian	Cambridge		GB
Mastrobattista; Enrico	Cambridge		GB

US-CL-CURRENT: 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 4. Document ID: US 20060153924 A1

L2: Entry 4 of 9 File: PGPB Jul 13, 2006

PGPUB-DOCUMENT-NUMBER: 20060153924
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060153924 A1

TITLE: Selection by compartmentalised screening

PUBLICATION-DATE: July 13, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Griffiths; Andrew David	Cambridge		GB
Abell; Chris	Cambridge		GB
Hollfelder; Florian	Cambridge		GB
Mastrobattista; Enrico	Cambridge		GB

US-CL-CURRENT: 424/490; 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 5. Document ID: US 20060078893 A1

L2: Entry 5 of 9 File: PGPB Apr 13, 2006

PGPUB-DOCUMENT-NUMBER: 20060078893
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060078893 A1

TITLE: Compartmentalised combinatorial chemistry by microfluidic control

PUBLICATION-DATE: April 13, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Griffiths; Andrew	Cambridge	MA	GB
Weitz; David	Bolton	CT	US
Link; Darren	Guilford	MA	US
Ahn; Keunho	Boston		US
Bibette; Jerome	Paris		FR

US-CL-CURRENT: 435/6; 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 6. Document ID: US 20050089890 A1

L2: Entry 6 of 9 File: PGPB Apr 28, 2005

PGPUB-DOCUMENT-NUMBER: 20050089890
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050089890 A1

TITLE: Multimolecular devices and drug delivery systems

PUBLICATION-DATE: April 28, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Cubicciotti, Roger S.	Montclair	NJ	US

US-CL-CURRENT: 435/6; 530/395

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 7. Document ID: US 20020034757 A1

L2: Entry 7 of 9 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034757
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034757 A1

TITLE: Single-molecule selection methods and compositions therefrom

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Cubicciotti, Roger S.	Montclair	NJ	US

US-CL-CURRENT: 435/6; 435/91.2, 536/22.1, 536/23.1, 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

---

☐ 8. Document ID: US 6762025 B2

L2: Entry 8 of 9 File: USPT Jul 13, 2004

US-PAT-NO: 6762025
DOCUMENT-IDENTIFIER: US 6762025 B2

TITLE: Single-molecule selection methods and compositions therefrom

DATE-ISSUED: July 13, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cubicciotti; Roger S.	Montclair	NJ		

US-CL-CURRENT: 435/6; 435/91.2, 536/22.1, 536/23.1, 536/24.3, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

---

☐ 9. Document ID: US 6287765 B1

L2: Entry 9 of 9 File: USPT Sep 11, 2001

US-PAT-NO: 6287765
DOCUMENT-IDENTIFIER: US 6287765 B1

TITLE: Methods for detecting and identifying single molecules

DATE-ISSUED: September 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Cubicciotti; Roger S. Montclair NJ

US-CL-CURRENT: 435/6; 435/91.2, 536/22.1, 536/23.1, 536/24.3, 536/24.5, 977/853

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
liposome same inkjet same (active or drug)	9

Display Format: - Change Format

Previous Page Next Page Go to Doc#

L4: Entry 39 of 47 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958378 A
**** See image for Certificate of Correction ****
TITLE: High dose liposomal aerosol formulations containing cyclosporin A or budesonide

Brief Summary Text (8):
Drug formulation also is a critical factor regulating aerosol output efficiency and aerodynamic properties of drug-liposomes. It has been discovered that drug-liposome output efficiency can be increased through the utilization of liposomes formulated with low phase transition temperatures (see Waldrep et al., J. of Aerosol Med. 7:1994 (1994) and Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). An additional method to increase aerosol drug-liposome output is to increase the drug and phospholipid reservoir concentrations. Nebulization of some drug-liposome formulations at greater than 50 mg/ml results in clogging of the nebulizer jets; yet empty liposomal formulations up to 150 mg/ml have been successfully nebulized (see Thomas, et al., Chest 99:1268-70 (1991)). Further, the aerosol performance (output and particle size) is influenced in part by physiochemical properties such as viscosity and surface tension. Such variables affect the maximal drug-liposome concentrations compatible with aerosol delivery via the jet nebulizer.

Detailed Description Text (4):
A second method of increasing aerosol drug-liposome output was to increase the reservoir concentration of drug and phospholipid in the liquid of the nebulizer reservoir. The cyclosporin A-DLPC liposome concentration of 5 mg cyclosporin A/37.5 mg per ml was successfully increased while achieving desired aerosol output in the range of 1-3 .mu.m mass median aerodynamic diameter (MMAD). Using a human lung deposition model, analysis of this aerosol indicated that approximately 3.2 mg of cyclosporin A theoretically would deposit within the lung after a single 15 minute inhalation. Studies by the University of Pittsburgh group of lung allograft patients treated with aerosolized cyclosporin A (dissolved in ethanol or propyleneglycol) demonstrated clinical improvement (reversal of graft rejection) when 20 mg of cyclosporin A was delivered to the lung. Using the available cyclosporin A-DLPC liposome system requires approximately 2 hours of aerosol inhalation to deliver this amount. Such a prolonged, daily inhalation interval would likely be cumbersome for the patient, and requires 8 recharges of the nebulizer reservoir. Therefore, the cyclosporin A-DLPC reservoir concentration needed to be increased. However, it is well known in the prior art that it was not possible to nebulize liposomes greater than 50 mg/ml, since greater concentrations resulted in clogging of the nebulizer jets.

Detailed Description Text (6):
As demonstrated in FIG. 2 in a simulated human lung model, 15 minutes with high-dose cyclosporin A-DLPC, the required time period to deliver a putative therapeutic dose in lung allograft patients would be approximately 45 minutes or less. Certainly, this interval is based on dosing results by other investigators using other cyclosporin A aerosols. Since cyclosporin A-liposomes are theoretically more effective at a lower dose and less toxic than cyclosporin A in ethanol or propylene glycol, the inhalation interval would likely be much less. Increasing the cyclosporin A-DLPC higher than about 30 mg cyclosporin A-225 mg DLPC proved inefficient.

Detailed Description Text (11):
Boehringer-Ingelheim has tested glucocorticoid liposomes in a nebulizer device. The design of their device called for the delivery of 100-200 .mu.g glucocorticoid per 20 .mu.l actuation. A simple math conversion demonstrates that 5,000 to 10,000 .mu.g/ml in the reservoir of the device would be required. In those experiments with the device, Budesonide in an ethanol vehicle was tested.

Detailed Description Text (26):
Aerodynamic particle sizing of the drug-liposome aerosols was determined as described in Waldrep et al., J. of Aerosol Med. 7:1994 (1994), using an Andersen 1 ACFM non-viable ambient particle sizing sampler (Graseby Andersen Instruments Inc., Atlanta, Ga.) as a simulator of the human lung (Andersen). Drug-liposome aerosols generated from the ATII nebulizer were collected using a vacuum pump (1 ACFM) by impaction on 8 aluminum stages at a standard sampling interval of 0.5 minutes for each experiment. Drug concentrations in aerosol droplets between 0-10 .mu.m sizes were collected on each stage (0=9.0-10.0 .mu.m; 1=5.8-9.0 .mu.m; 2=4.7-5.8 .mu.m; 3=3.3-4.7 .mu.m; 4=2.1-3.3 .mu.m; 5=1.1-2.1 .mu.m; 6=0.65-1.1 .mu.m; 7=0.43-0.65 .mu.m) and determined after elution with 10 ml of ethanol or methanol and HPLC analysis. An USP artificial throat attached to the inlet port of the impactor is used to remove few aerosol particles larger than 10 .mu.m. The final stage used a glass fiber collection filter. After determination of the drug concentrations for each stage by HPLC, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the drug-liposomes was calculated on a log probability scale with the effective cutoff diameter as the ordinate and the cumulative percent less than the size range (by concentration) as the abscissa (KaleidaGraph 3.0). The MMAD and GSD are determined by the liposomal drug content distributed within the array of droplets comprising the aerosol (see Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). The droplet array rather than the liposome size determined the MMAD and the GSD. The validity of this method for calculation of MMAD & GSD was verified independently using a Model 3300 TSI Laser Aerosol Particle Sizer.

Detailed Description Text (38):
6. A Sep-Pak C18 column (Waters Sep-Pak Light for single mouse tissue) was prepared and was washed with 5 ml 95% Ethanol and 5 ml ultra pure water. The sample was added slowly and washed with 5 ml ultra pure water, and 5 ml 50% Acetonitrile

Detailed Description Text (45):
The HPLC assay was utilized for multiple purposes to determine: the Budesonide content of liposome formulations, the encapsulation efficiency, and the Budesonide content of aerosol samples obtained with the lung simulator. Budesonide concentrations were determined by HPLC analysis using a Waters WISP 717 autosampler and a Waters Nova-Pak C18 (3.9.times.150 mm) column at room temperature. Peak detection was performed at 238 nanometers using a variable UV/Vis wavelength detector with quantification by a Waters Millenium 2010 Chromatography Manager Version 2.15. The mobile phase utilized for these studies was 50:50 ethanol/water at a flow rate of 0.6 ml per minute (see Andersson & Ryrfeldt, J Pharm Pharmacol 36:763-65 (1984)) Samples for analysis were dissolved directly into ethanol (to solubilize the liposomes). Drug standards were prepared from ethanol stocks kept at -80.degree. C.

Detailed Description Text (51):
A modification of the HPLC protocol of Grit and Commelin Chem. & Phys. of Lipids 62:113-22 (1992), was used. A Waters 717 WISP automatic sample injector and a Sperisorb S5 amino column (25 cm.times.4.6 mm, 5 .mu.m) was utilized with acetonitrile, methanol, and 10 mM ammonium/trifluoroacetic acid, pH 4.8 (64:28:8 v:v:v) mobile phase. Peaks were detected with a mass evaporative detector (SEDEX 55, Sedre, France) and quantified with the Waters Millenium 2010 Chromatography Manager Version 2.15. Samples for analysis were dissolved directly in ethanol or

methanol (to solubilize the liposomes).

Previous Doc Next Doc Go to Doc#

L4: Entry 39 of 47 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958378 A
**** See image for Certificate of Correction ****
TITLE: High dose liposomal aerosol formulations containing cyclosporin A or budesonide

Brief Summary Text (8):
Drug formulation also is a critical factor regulating aerosol output efficiency and aerodynamic properties of drug-liposomes. It has been discovered that drug-liposome output efficiency can be increased through the utilization of liposomes formulated with low phase transition temperatures (see Waldrep et al., J. of Aerosol Med. 7:1994 (1994) and Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). An additional method to increase aerosol drug-liposome output is to increase the drug and phospholipid reservoir concentrations. Nebulization of some drug-liposome formulations at greater than 50 mg/ml results in clogging of the nebulizer jets; yet empty liposomal formulations up to 150 mg/ml have been successfully nebulized (see Thomas, et al., Chest 99:1268-70 (1991)). Further, the aerosol performance (output and particle size) is influenced in part by physiochemical properties such as viscosity and surface tension. Such variables affect the maximal drug-liposome concentrations compatible with aerosol delivery via the jet nebulizer.

Detailed Description Text (4):
A second method of increasing aerosol drug-liposome output was to increase the reservoir concentration of drug and phospholipid in the liquid of the nebulizer reservoir. The cyclosporin A-DLPC liposome concentration of 5 mg cyclosporin A/37.5 mg per ml was successfully increased while achieving desired aerosol output in the range of 1-3 .mu.m mass median aerodynamic diameter (MMAD). Using a human lung deposition model, analysis of this aerosol indicated that approximately 3.2 mg of cyclosporin A theoretically would deposit within the lung after a single 15 minute inhalation. Studies by the University of Pittsburgh group of lung allograft patients treated with aerosolized cyclosporin A (dissolved in ethanol or propyleneglycol) demonstrated clinical improvement (reversal of graft rejection) when 20 mg of cyclosporin A was delivered to the lung. Using the available cyclosporin A-DLPC liposome system requires approximately 2 hours of aerosol inhalation to deliver this amount. Such a prolonged, daily inhalation interval would likely be cumbersome for the patient, and requires 8 recharges of the nebulizer reservoir. Therefore, the cyclosporin A-DLPC reservoir concentration needed to be increased. However, it is well known in the prior art that it was not possible to nebulize liposomes greater than 50 mg/ml, since greater concentrations resulted in clogging of the nebulizer jets.

Detailed Description Text (6):
As demonstrated in FIG. 2 in a simulated human lung model, 15 minutes with high-dose cyclosporin A-DLPC, the required time period to deliver a putative therapeutic dose in lung allograft patients would be approximately 45 minutes or less. Certainly, this interval is based on dosing results by other investigators using other cyclosporin A aerosols. Since cyclosporin A-liposomes are theoretically more effective at a lower dose and less toxic than cyclosporin A in ethanol or propylene glycol, the inhalation interval would likely be much less. Increasing the cyclosporin A-DLPC higher than about 30 mg cyclosporin A-225 mg DLPC proved inefficient.

Detailed Description Text (11):
Boehringer-Ingelheim has tested glucocorticoid liposomes in a nebulizer device. The design of their device called for the delivery of 100-200 .mu.g glucocorticoid per 20 .mu.l actuation. A simple math conversion demonstrates that 5,000 to 10,000 .mu.g/ml in the reservoir of the device would be required. In those experiments with the device, Budesonide in an ethanol vehicle was tested.

Detailed Description Text (26):
Aerodynamic particle sizing of the drug-liposome aerosols was determined as described in Waldrep et al., J. of Aerosol Med. 7:1994 (1994), using an Andersen 1 ACFM non-viable ambient particle sizing sampler (Graseby Andersen Instruments Inc., Atlanta,.Ga.) as a simulator of the human lung (Andersen). Drug-liposome aerosols generated from the ATII nebulizer were collected using a vacuum pump (1 ACFM) by impaction on 8 aluminum stages at a standard sampling interval of 0.5 minutes for each experiment. Drug concentrations in aerosol droplets between 0-10 .mu.m sizes were collected on each stage (0=9.0-10.0 .mu.m; 1=5.8-9.0 .mu.m; 2=4.7-5.8 .mu.m; 3=3.3-4.7 .mu.m; 4=2.1-3.3 .mu.m; 5=1.1-2.1 .mu.m; 6=0.65-1.1 .mu.m; 7=0.43-0.65 .mu.m) and determined after elution with 10 ml of ethanol or methanol and HPLC analysis. An USP artificial throat attached to the inlet port of the impactor is used to remove few aerosol particles larger than 10 .mu.m. The final stage used a glass fiber collection filter. After determination of the drug concentrations for each stage by HPLC, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the drug-liposomes was calculated on a log probability scale with the effective cutoff diameter as the ordinate and the cumulative percent less than the size range (by concentration) as the abscissa (KaleidaGraph 3.0). The MMAD and GSD are determined by the liposomal drug content distributed within the array of droplets comprising the aerosol (see Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). The droplet array rather than the liposome size determined the MMAD and the GSD. The validity of this method for calculation of MMAD & GSD was verified independently using a Model 3300 TSI Laser Aerosol Particle Sizer.

Detailed Description Text (38):
6. A Sep-Pak C18 column (Waters Sep-Pak Light for single mouse tissue) was prepared and was washed with 5 ml 95% Ethanol and 5 ml ultra pure water. The sample was added slowly and washed with 5 ml ultra pure water, and 5 ml 50% Acetonitrile

Detailed Description Text (45):
The HPLC assay was utilized for multiple purposes to determine: the Budesonide content of liposome formulations, the encapsulation efficiency, and the Budesonide content of aerosol samples obtained with the lung simulator. Budesonide concentrations were determined by HPLC analysis using a Waters WISP 717 autosampler and a Waters Nova-Pak C18 (3.9.times.150 mm) column at room temperature. Peak detection was performed at 238 nanometers using a variable UV/Vis wavelength detector with quantification by a Waters Millenium 2010 Chromatography Manager Version 2.15. The mobile phase utilized for these studies was 50:50 ethanol/water at a flow rate of 0.6 ml per minute (see Andersson & Ryrfeldt, J Pharm Pharmacol 36:763-65 (1984)) Samples for analysis were dissolved directly into ethanol (to solubilize the liposomes). Drug standards were prepared from ethanol stocks kept at -80.degree. C.

Detailed Description Text (51):
A modification of the HPLC protocol of Grit and Commelin Chem. & Phys. of Lipids 62:113-22 (1992), was used. A Waters 717 WISP automatic sample injector and a Sperisorb S5 amino column (25 cm.times.4.6 mm, 5 .mu.m) was utilized with acetonitrile, methanol, and 10 mM ammonium/trifluoroacetic acid, pH 4.8 (64:28:8 v:v:v) mobile phase. Peaks were detected with a mass evaporative detector (SEDEX 55, Sedre, France) and quantified with the Waters Millenium 2010 Chromatography Manager Version 2.15. Samples for analysis were dissolved directly in ethanol or

methanol (to solubilize the liposomes).

Previous Doc Next Doc Go to Doc#

L4: Entry 39 of 47 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958378 A

**** See image for Certificate of Correction ****

TITLE: High dose liposomal aerosol formulations containing cyclosporin A or budesonide

Brief Summary Text (8):

Drug formulation also is a critical factor regulating aerosol output efficiency and aerodynamic properties of drug-liposomes. It has been discovered that drug-liposome output efficiency can be increased through the utilization of liposomes formulated with low phase transition temperatures (see Waldrep et al., J. of Aerosol Med. 7:1994 (1994) and Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). An additional method to increase aerosol drug-liposome output is to increase the drug and phospholipid reservoir concentrations. Nebulization of some drug-liposome formulations at greater than 50 mg/ml results in clogging of the nebulizer jets; yet empty liposomal formulations up to 150 mg/ml have been successfully nebulized (see Thomas, et al., Chest 99:1268-70 (1991)). Further, the aerosol performance (output and particle size) is influenced in part by physiochemical properties such as viscosity and surface tension. Such variables affect the maximal drug-liposome concentrations compatible with aerosol delivery via the jet nebulizer.

Detailed Description Text (4):

A second method of increasing aerosol drug-liposome output was to increase the reservoir concentration of drug and phospholipid in the liquid of the nebulizer reservoir. The cyclosporin A-DLPC liposome concentration of 5 mg cyclosporin A/37.5 mg per ml was successfully increased while achieving desired aerosol output in the range of 1-3 .mu.m mass median aerodynamic diameter (MMAD). Using a human lung deposition model, analysis of this aerosol indicated that approximately 3.2 mg of cyclosporin A theoretically would deposit within the lung after a single 15 minute inhalation. Studies by the University of Pittsburgh group of lung allograft patients treated with aerosolized cyclosporin A (dissolved in ethanol or propyleneglycol) demonstrated clinical improvement (reversal of graft rejection) when 20 mg of cyclosporin A was delivered to the lung. Using the available cyclosporin A-DLPC liposome system requires approximately 2 hours of aerosol inhalation to deliver this amount. Such a prolonged, daily inhalation interval would likely be cumbersome for the patient, and requires 8 recharges of the nebulizer reservoir. Therefore, the cyclosporin A-DLPC reservoir concentration needed to be increased. However, it is well known in the prior art that it was not possible to nebulize liposomes greater than 50 mg/ml, since greater concentrations resulted in clogging of the nebulizer jets.

Detailed Description Text (6):

As demonstrated in FIG. 2 in a simulated human lung model, 15 minutes with high-dose cyclosporin A-DLPC, the required time period to deliver a putative therapeutic dose in lung allograft patients would be approximately 45 minutes or less. Certainly, this interval is based on dosing results by other investigators using other cyclosporin A aerosols. Since cyclosporin A-liposomes are theoretically more effective at a lower dose and less toxic than cyclosporin A in ethanol or propylene glycol, the inhalation interval would likely be much less. Increasing the cyclosporin A-DLPC higher than about 30 mg cyclosporin A-225 mg DLPC proved inefficient.

Detailed Description Text (11):
Boehringer-Ingelheim has tested glucocorticoid liposomes in a nebulizer device. The design of their device called for the delivery of 100-200 .mu.g glucocorticoid per 20 .mu.l actuation. A simple math conversion demonstrates that 5,000 to 10,000 .mu.g/ml in the reservoir of the device would be required. In those experiments with the device, Budesonide in an ethanol vehicle was tested.

Detailed Description Text (26):
Aerodynamic particle sizing of the drug-liposome aerosols was determined as described in Waldrep et al., J. of Aerosol Med. 7:1994 (1994), using an Andersen 1 ACFM non-viable ambient particle sizing sampler (Graseby Andersen Instruments Inc., Atlanta, Ga.) as a simulator of the human lung (Andersen). Drug-liposome aerosols generated from the ATII nebulizer were collected using a vacuum pump (1 ACFM) by impaction on 8 aluminum stages at a standard sampling interval of 0.5 minutes for each experiment. Drug concentrations in aerosol droplets between 0-10 .mu.m sizes were collected on each stage (0=9.0-10.0 .mu.m; 1=5.8-9.0 .mu.m; 2=4.7-5.8 .mu.m; 3=3.3-4.7 .mu.m; 4=2.1-3.3 .mu.m; 5=1.1-2.1 .mu.m; 6=0.65-1.1 .mu.m; 7=0.43-0.65 .mu.m) and determined after elution with 10 ml of ethanol or methanol and HPLC analysis. An USP artificial throat attached to the inlet port of the impactor is used to remove few aerosol particles larger than 10 .mu.m. The final stage used a glass fiber collection filter. After determination of the drug concentrations for each stage by HPLC, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the drug-liposomes was calculated on a log probability scale with the effective cutoff diameter as the ordinate and the cumulative percent less than the size range (by concentration) as the abscissa (KaleidaGraph 3.0). The MMAD and GSD are determined by the liposomal drug content distributed within the array of droplets comprising the aerosol (see Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). The droplet array rather than the liposome size determined the MMAD and the GSD. The validity of this method for calculation of MMAD & GSD was verified independently using a Model 3300 TSI Laser Aerosol Particle Sizer.

Detailed Description Text (38):
6. A Sep-Pak C18 column (Waters Sep-Pak Light for single mouse tissue) was prepared and was washed with 5 ml 95% Ethanol and 5 ml ultra pure water. The sample was added slowly and washed with 5 ml ultra pure water, and 5 ml 50% Acetonitrile

Detailed Description Text (45):
The HPLC assay was utilized for multiple purposes to determine: the Budesonide content of liposome formulations, the encapsulation efficiency, and the Budesonide content of aerosol samples obtained with the lung simulator. Budesonide concentrations were determined by HPLC analysis using a Waters WISP 717 autosampler and a Waters Nova-Pak C18 (3.9.times.150 mm) column at room temperature. Peak detection was performed at 238 nanometers using a variable UV/Vis wavelength detector with quantification by a Waters Millenium 2010 Chromatography Manager Version 2.15. The mobile phase utilized for these studies was 50:50 ethanol/water at a flow rate of 0.6 ml per minute (see Andersson & Ryrfeldt, J Pharm Pharmacol 36:763-65 (1984)) Samples for analysis were dissolved directly into ethanol (to solubilize the liposomes). Drug standards were prepared from ethanol stocks kept at -80.degree. C.

Detailed Description Text (51):
A modification of the HPLC protocol of Grit and Commelin Chem. & Phys. of Lipids 62:113-22 (1992), was used. A Waters 717 WISP automatic sample injector and a Sperisorb S5 amino column (25 cm.times.4.6 mm, 5 .mu.m) was utilized with acetonitrile, methanol, and 10 mM ammonium/trifluoroacetic acid, pH 4.8 (64:28:8 v:v:v) mobile phase. Peaks were detected with a mass evaporative detector (SEDEX 55, Sedre, France) and quantified with the Waters Millenium 2010 Chromatography Manager Version 2.15. Samples for analysis were dissolved directly in ethanol or

methanol (to solubilize the liposomes).

Previous Doc Next Doc Go to Doc#

L4: Entry 39 of 47 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958378 A
**** See image for Certificate of Correction ****
TITLE: High dose liposomal aerosol formulations containing cyclosporin A or budesonide

Brief Summary Text (8):
Drug formulation also is a critical factor regulating aerosol output efficiency and aerodynamic properties of drug-liposomes. It has been discovered that drug-liposome output efficiency can be increased through the utilization of liposomes formulated with low phase transition temperatures (see Waldrep et al., J. of Aerosol Med. 7:1994 (1994) and Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). An additional method to increase aerosol drug-liposome output is to increase the drug and phospholipid reservoir concentrations. Nebulization of some drug-liposome formulations at greater than 50 mg/ml results in clogging of the nebulizer jets; yet empty liposomal formulations up to 150 mg/ml have been successfully nebulized (see Thomas, et al., Chest 99:1268-70 (1991)). Further, the aerosol performance (output and particle size) is influenced in part by physiochemical properties such as viscosity and surface tension. Such variables affect the maximal drug-liposome concentrations compatible with aerosol delivery via the jet nebulizer.

Detailed Description Text (4):
A second method of increasing aerosol drug-liposome output was to increase the reservoir concentration of drug and phospholipid in the liquid of the nebulizer reservoir. The cyclosporin A-DLPC liposome concentration of 5 mg cyclosporin A/37.5 mg per ml was successfully increased while achieving desired aerosol output in the range of 1-3 .mu.m mass median aerodynamic diameter (MMAD). Using a human lung deposition model, analysis of this aerosol indicated that approximately 3.2 mg of cyclosporin A theoretically would deposit within the lung after a single 15 minute inhalation. Studies by the University of Pittsburgh group of lung allograft patients treated with aerosolized cyclosporin A (dissolved in ethanol or propyleneglycol) demonstrated clinical improvement (reversal of graft rejection) when 20 mg of cyclosporin A was delivered to the lung. Using the available cyclosporin A-DLPC liposome system requires approximately 2 hours of aerosol inhalation to deliver this amount. Such a prolonged, daily inhalation interval would likely be cumbersome for the patient, and requires 8 recharges of the nebulizer reservoir. Therefore, the cyclosporin A-DLPC reservoir concentration needed to be increased. However, it is well known in the prior art that it was not possible to nebulize liposomes greater than 50 mg/ml, since greater concentrations resulted in clogging of the nebulizer jets.

Detailed Description Text (6):
As demonstrated in FIG. 2 in a simulated human lung model, 15 minutes with high-dose cyclosporin A-DLPC, the required time period to deliver a putative therapeutic dose in lung allograft patients would be approximately 45 minutes or less. Certainly, this interval is based on dosing results by other investigators using other cyclosporin A aerosols. Since cyclosporin A-liposomes are theoretically more effective at a lower dose and less toxic than cyclosporin A in ethanol or propylene glycol, the inhalation interval would likely be much less. Increasing the cyclosporin A-DLPC higher than about 30 mg cyclosporin A-225 mg DLPC proved inefficient.

Detailed Description Text (11):
Boehringer-Ingelheim has tested glucocorticoid liposomes in a nebulizer device. The design of their device called for the delivery of 100-200 .mu.g glucocorticoid per 20 .mu.l actuation. A simple math conversion demonstrates that 5,000 to 10,000 .mu.g/ml in the reservoir of the device would be required. In those experiments with the device, Budesonide in an ethanol vehicle was tested.

Detailed Description Text (26):
Aerodynamic particle sizing of the drug-liposome aerosols was determined as described in Waldrep et al., J. of Aerosol Med. 7:1994 (1994), using an Andersen 1 ACFM non-viable ambient particle sizing sampler (Graseby Andersen Instruments Inc., Atlanta, Ga.) as a simulator of the human lung (Andersen). Drug-liposome aerosols generated from the ATII nebulizer were collected using a vacuum pump (1 ACFM) by impaction on 8 aluminum stages at a standard sampling interval of 0.5 minutes for each experiment. Drug concentrations in aerosol droplets between 0-10 .mu.m sizes were collected on each stage (0=9.0-10.0 .mu.m; 1=5.8-9.0 .mu.m; 2=4.7-5.8 .mu.m; 3=3.3-4.7 .mu.m; 4=2.1-3.3 .mu.m; 5=1.1-2.1 .mu.m; 6=0.65-1.1 .mu.m; 7=0.43-0.65 .mu.m) and determined after elution with 10 ml of ethanol or methanol and HPLC analysis. An USP artificial throat attached to the inlet port of the impactor is used to remove few aerosol particles larger than 10 .mu.m. The final stage used a glass fiber collection filter. After determination of the drug concentrations for each stage by HPLC, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the drug-liposomes was calculated on a log probability scale with the effective cutoff diameter as the ordinate and the cumulative percent less than the size range (by concentration) as the abscissa (KaleidaGraph 3.0). The MMAD and GSD are determined by the liposomal drug content distributed within the array of droplets comprising the aerosol (see Waldrep et al., Int'l J. of Pharmaceutics 97:205-12 (1993)). The droplet array rather than the liposome size determined the MMAD and the GSD. The validity of this method for calculation of MMAD & GSD was verified independently using a Model 3300 TSI Laser Aerosol Particle Sizer.

Detailed Description Text (38):
6. A Sep-Pak C18 column (Waters Sep-Pak Light for single mouse tissue) was prepared and was washed with 5 ml 95% Ethanol and 5 ml ultra pure water. The sample was added slowly and washed with 5 ml ultra pure water, and 5 ml 50% Acetonitrile

Detailed Description Text (45):
The HPLC assay was utilized for multiple purposes to determine: the Budesonide content of liposome formulations, the encapsulation efficiency, and the Budesonide content of aerosol samples obtained with the lung simulator. Budesonide concentrations were determined by HPLC analysis using a Waters WISP 717 autosampler and a Waters Nova-Pak C18 (3.9.times.150 mm) column at room temperature. Peak detection was performed at 238 nanometers using a variable UV/Vis wavelength detector with quantification by a Waters Millenium 2010 Chromatography Manager Version 2.15. The mobile phase utilized for these studies was 50:50 ethanol/water at a flow rate of 0.6 ml per minute (see Andersson & Ryrfeldt, J Pharm Pharmacol 36:763-65 (1984)) Samples for analysis were dissolved directly into ethanol (to solubilize the liposomes). Drug standards were prepared from ethanol stocks kept at -80.degree. C.

Detailed Description Text (51):
A modification of the HPLC protocol of Grit and Commelin Chem. & Phys. of Lipids 62:113-22 (1992), was used. A Waters 717 WISP automatic sample injector and a Sperisorb S5 amino column (25 cm.times.4.6 mm, 5 .mu.m) was utilized with acetonitrile, methanol, and 10 mM ammonium/trifluoroacetic acid, pH 4.8 (64:28:8 v:v:v) mobile phase. Peaks were detected with a mass evaporative detector (SEDEX 55, Sedre, France) and quantified with the Waters Millenium 2010 Chromatography Manager Version 2.15. Samples for analysis were dissolved directly in ethanol or

methanol (to solubilize the liposomes).

Previous Doc Next Doc Go to Doc#